Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

# Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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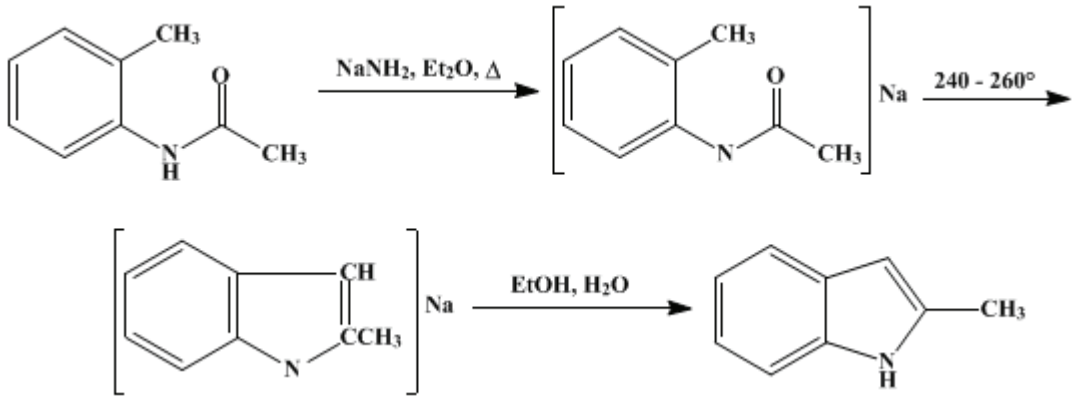
# 2-METHYLINDOLE

## [Indole, 2-methyl-]

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## 1. Procedure

In a 1-l. Claisen flask is placed a mixture of 64 g. of finely divided sodium amide (Note 1) and 100 g. of acetyl-*o*-toluidine (Note 2). About 50 ml. of dry ether is added (Note 3), and the apparatus is swept out with dry nitrogen. Then, with a slow current of nitrogen passing through the mixture, the reaction flask (Note 4) is heated in a metal bath (Note 5). The temperature is raised to 240–260° over a 30-minute period and is maintained in this range for 10 minutes. A vigorous evolution of gas occurs, the cessation of which indicates that the reaction is complete (Note 6). The metal bath is removed, the flask is allowed to cool, and 50 ml. of 95% ethanol and 250 ml. of warm (about 50°) water are added, successively, to the reaction mixture. The decomposition of the sodium derivative of 2-methylindole, and of any excess sodium amide, is completed by warming the mixture gently with a Bunsen burner. The cooled reaction mixture is extracted with two 200-ml. portions of ether (Note 7). The combined ether extracts are filtered, and the filtrate is concentrated to about 125 ml. The solution is then transferred to a 250-ml. modified Claisen flask and distilled. The 2-methylindole distils at 119–126° /3–4 mm. as a water-white liquid, which rapidly solidifies in the receiver to a white crystalline mass. This product melts at 56–57°. The yield is 70–72 g. (80–83%) (Note 8).

The product may be further purified by dissolving it in 100 ml. of methanol, adding 30 ml. of water, and allowing the solution to stand in the ice chest for 5 hours. The pure white plates (52 g.) melt at 59°. An additional 10 g. may be recovered by cooling the filtrate after it has been diluted with about 20 ml. of water.

## 2. Notes

1. The sodium amide was ground in an open mortar, and at no time was difficulty experienced. As a precautionary measure, the grinding could be carried out under ether.
2. Acetyl-*o*-toluidine, m.p. 110–111°, obtained from the Eastman Kodak Company, was used. After the reactants are introduced into the flask, they should be mixed thoroughly with a long spatula.
3. The ether is added to facilitate the formation of the sodium salt of the amide.
4. It is advisable to cover the bottom of the reaction flask with soot, to prevent the metal from adhering to the glass.
5. Sand and salt baths are not satisfactory.
6. Reaction begins when the bath temperature has risen to approximately 200°. Frothing occurs, and the froth solidifies. The checkers found it necessary to stir the solidified froth into the reaction mixture, so that heating of the whole mass could be uniform. This stirring is necessary throughout—i.e., from the

beginning of vigorous gas evolution until completion of the period of heating.
7. The indole may be isolated, less conveniently, by steam distillation; the crystalline product (m.p. about 56–57°) can be filtered from the cold distillate.
8. The method described here is of general application to substituted acetyl- and benzoyl-*o*-toluidines.

## 3. Discussion

The method described here is a modification of Verley's procedure.[1] 2-Methylindole may also be prepared by the treatment of acetone phenylhydrazone with zinc chloride at 180°.[2]

The cyclization of acetyl-*o*-toluidine has been reported to occur in low yield on distillation with zinc dust.[3] Better yields have been obtained by heating the toluidide with sodium ethoxide or with barium oxide in a current of hydrogen at 360–380°.[4] A vapor-phase cyclization over a silica-alumina catalyst has also been reported.[5]

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## References and Notes


1. Verley, *Bull. soc. chim. France*, (4) **35**, 1039 (1924).
2. Fischer, *Ann.*, **236**, 116 (1886); *Ber.*, **19**, 1563 (1886); Marion and Oldfield, *Can. J. Research*, **25B**, 1 (1947).
3. Mauthner and Suida, *Monatsh.*, **7**, 230, 237 (1886).
4. Madelung, Ger. pat. 262,327 [*Frdl.*, **11**, 278 (1912–1914)]; *Ber.*, **45**, 1128 (1912).
5. Ger. pat. 458,383 [*Frdl.*, **16**, 709 (1931)].


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## Appendix
## Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

sodium derivative of 2-methylindole

acetyl- and benzoyl-o-toluidines

toluidide

silica-alumina

ethanol (64-17-5)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

barium oxide

nitrogen (7727-37-9)

zinc (7440-66-6)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

zinc chloride (7646-85-7)

sodium amide (7782-92-5)

Indole (120-72-9)

2-Methylindole,
Indole, 2-methyl- (95-20-5)

acetone phenylhydrazone (103-02-6)

acetyl-o-toluidine (120-66-1)